REMARKS

Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made. In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Appendix A

Version With Markings to Show Changes Made

In reference to the amendments made herein to the specification, additions appear as double-underlined text, as indicated below:

In The Specification:

At page 1, lines 4-5

This application is a divisional of U.S. Patent Application Serial No. 08/794,851, filed February 4, 1997, which claims the benefit of U.S. Provisional Patent Application Serial No. 60/011,359, filed February 9, 1996.

At page 17, lines 9-29:

Figure 6 is a flow diagram of a PCR/LDR process, in accordance with the present invention, where insertions (top left set of probes) and deletions (bottom right set of probes) are distinguished. On the left, the normal sequence contains 5 A's in a polyA tract. The mutant sequence has an additional 2As inserted into the tract. Therefore, the LDR products with addressable array-specific portions Z1 (representing the normal sequence) and Z3 (representing a 2 base pair insertion) would be fluorescently labeled by ligation to the common primer. While the LDR process (e.g., using a thermostable ligase enzyme) has no difficulty distinguishing single base insertions or deletions in mononucleotide repeats, allele-specific PCR is unable to distinguish such differences, because the 3' base remains the same for both alleles. On the right, the normal sequence is a (CA)5 repeat (i.e. CACACACACA (SEQ. ID. No. 1)). The mutant contains two less CA bases than the normal sequence (i.e. CACACA). These would be detected as fluorescent LDR products at the addressable array-specific portions Z8 (representing the normal sequence) and Z6 (representing the 2 CA deletion) addresses. The resistance of various infectious agents to drugs can also be determined using the present invention. In Figure 6, the presence of ligated product sequences, as indicated by fluorescent label F, at the address having capture oligonucleotides complementary to Z1 and Z3 demonstrates the presence of both the normal and mutant poly A sequences. Similarly, the presence of ligated product sequences, as indicated by fluorescent label F, at the address having capture oligonucleotides complementary to Z6 and

Z8 demonstrates the presence of both the normal CA repeat and a sequence with one repeat unit deleted.

At page 40, lines 14-34:

To illustrate the concept, a subset of six of the 36 tetramer sequences were used to construct arrays: 1 = TGCG; 2 = ATCG; 3 = CAGC; 4 = GGTA; 5 = GACC; and 6 = ACCT. This unique set of tetramers can be used as design modules for the required 24-mer addressable array-specific portion and 24-mer complementary capture oligonucleotide address sequences. This embodiment involves synthesis of five addressable array-specific portion (sequences listed in Table 2). Note that the numbering scheme for tetramers allows abbreviation of each portion (referred to as "Zip #") as a string of six numbers (referred to as "zip code").

Table 2. List of all 5 DNA/PNA oligonucleotide address sequences.

Zip #	Zip code	Sequence (5' → 3' or NH_2 → COOH)	G+C
Zip11	1-4-3-6-6-1	TGCG-GGTA-CAGC-ACCT-ACCT-TGCG (SEQ. ID. No. 2)	15
Zip12	2-4-4-6-1-1	ATCG-GGTA-GGTA-ACCT-TGCG-TGCG (SEQ. ID. No. 3)	14
Zip13	3-4-5-6-2-1	CAGC-GGTA-GACC-ACCT-ATCG-TGCG (SEQ. ID. No. 4)	15
Zip14	4-4-6-6-3-1	GGTA-GGTA-ACCT-ACCT-CAGC-TGCG (SEQ. ID. No. 5)	14
Zip15	5-4-1-6-4-1	GACC-GGTA-TGCG-ACCT-GGTA-TGCG (SEQ. ID. No. 6)	15

Each of these oligomers contains a hexaethylene oxide linker arm on their 5' termini [P. Grossman, et al., Nucl. Acids Res., 22:4527-4534 (1994), which is hereby incorporated by reference], and ultimate amino-functions suitable for attachment onto the surfaces of glass slides, or alternative materials. Conjugation methods will depend on the free surface functional groups [Y. Zhang, et al., Nucleic Acids Res., 19:3929-3933 (1991) and Z. Guo, et al., Nucleic Acids Res., 34:5456-5465 (1994), which are hereby incorporated by reference].

At page 42, lines 17-25:

This concept is illustrated below using the two addresses, Zip 12 and Zip 14. These two addresses are the most related among the 25 addresses schematically represented in Figures 18 and 20 (discussed *infra*). These two addresses have in common tetramers on every alternating position (shown as underlined):

Zip 12 (2-4-4-6-1-1) = 24 mer
5' - ATCG GGTA GGTA ACCT TGCG TGCG-3' (SEQ. ID. No. 7)
Zip 14 (4-4-6-6-3-1) = 24 mer

5' - GGTA GGTA ACCT ACCT CAGC TGCG-3' (SEQ. ID. No. 8)

At page 42, lines 27-33:

In addition, they have in common a string of 12 nucleotides, as well as the last four in common (shown as underlined):

Zip 12 (2-4-4-6-1-1) = 24 mer
5' - ATCG GGTA GGTA ACCT TGCG TGCG-3' (SEQ. ID. No. 9)
Zip 14 (4-4-6-6-3-1) = 24 mer
5' - GGTA GGTA ACCT ACCT CAGC TGCG-3' (SEQ. ID. No. 10)

At page 43, lines 1-7:

Furthermore, for other capture oligonucleotides, such as Zip 3, the number of shared nucleotides is much lower (shown as underlined):

Zip 12 (2-4-4-6-1-1) = 24 mer
5' - ATCG GGTA GGTA ACCT TGCG TGCG-3' (SEQ. ID. No. 11)
Zip 3 (3-6-5-2-2-3) = 24 mer
5' - CAGC ACCT GACC ATCG ATCG CAGC-3' (SEQ. ID. No. 12)

At page 55, lines 9-24:

Typically, 10 pmol of each of the oligonucleotides comp 12 and comp 14 (see Table 3) were 5' end labeled in a volume of 20 µl containing 10 units of T4 polynucleotide kinase (New England Biolabs, Beverly, MA), 2.22 MBq (60 µCi) [γ–^{32}P] ATP, 50 mM Tris-HCl, pH 8, 10 mM $MgCl_2$, 1 mM EDTA, and 10 mM dithiothreitol, according to a slightly modified standard procedure described in the literature. Unincorporated radioactive nucleotides were removed by filtration over a column containing superfine DNA grade Sephadex G-25 (Pharmacia, Piscataway, NJ). The Sephadex was preswollen overnight at 4 °C in 10 mM ammonium acetate. The labeled oligonucleotide probes were dried in vacuum and dissolved in hybridization solution (0.5 M Na_2HPO_4 [pH 7.2], 1% crystalline grade BSA, 1 mM EDTA, 7% SDS). The specific activity of the labeled oligonucleotide probes comp 12 and comp 14 was 2.86 x 10^6 cpm/pmol and 2.43 x 10^6 cpm/pmol, respectively.

Table 3. Oligonucleotides used (5' to 3')

12	Aminolink- spacer 18- ATC GGG TAG GTA ACC TTG CGT GCG (SEQ. ID. No. 13)
14	Aminolink- spacer 18- GGT AGG TAA CCT ACC TCA GCT GCG (SEQ. ID. No. 14)
comp 12	CGC ACG CAA GGT TAC CTA CCC GAT (SEQ. ID. No. 15)
comp 14	CGC AGC TGA GGT AGG TTA CCT ACC (SEQ. ID. No. 16)